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Letter to the Editor

Mapping of the Loci for Mental Retardation Syndromes in the Distal Xq

To the Editor:

We constructed a deletion map of the distal Xq, using previously reported male interstitial deletions within Xq27–Xqter. The map consists of 12 large interstitial deletions, ranging from 100–9,000 kb. All but one fall within Xq27→proximal Xq28, forming a "deletion contig" between DXS51 (Xq26.3) and DXS455 (proximal 1/3 of Xq28). The region contains only a few genes, most of which are implicated in mental retardation (MR). Some of the deletions span more than one MR locus. The phenotype of affected males is typically limited to mental impairment unless the F9, IDS, or F8 gene is included in the deletion.

In the distal ⅔ of Xq28 only one large deletion of about 300 kb has been reported, and those remaining are small, intragenic deletions of <1 kb. This indicates that most deletions in this region are male-lethal.

The map allows us to narrow the location of several loci for syndromic MR [Neri et al., 1994], and facilitates mapping of new genes in the distal Xq.

Recent work at the junction of Xq27.3 and Xq28 demonstrates that this small region contains several loci implicated in mental retardation (MR): fragile-site mental retardation 1 (FMR1 and FRAXA) [Oostra and Verkerk, 1992]; fragile-site mental retardation 2 (FMR2 and FRAXE) [Knight et al., 1993; Gecz et al., 1996; Gu et al., 1996]; a locus around DXS296 [Gedeon et al., 1995] which may be the same as FMR2 [Gu et al., 1996]; iduronate 2-sulfatase (IDS) [Wilson et al., 1990, 1991]; and fragile-site F (FRAXF) [Hirst et al., 1993; Ritchie et al., 1994]. Thus, an abundance of MR loci is being found in the vast and otherwise void area of 15 Mb comprising Xq27→proximal Xq28, where only two other genes (cerebellar degeneration-related autoantigen 1 (CDR1) [Hirst et al., 1991], and myotubular myopathy 1 (MTM1) [Dahl et al., 1995] have been assigned. It remains to be seen whether this clustering of MR genes reflects local peculiarities of the DNA sequence, or an ascertainment bias caused by the specific search for MR genes in the vicinity of the FMR1 gene. It is noteworthy that in the entire region Xq27–Xqter, every deletion found in a male is associated with mental retardation. Furthermore, some phenotypes may result from the absence of more than one MR gene. It should be considered, therefore, that the region Xq27→proximal Xq28 seems to be devoid of vital genes, and thus even very large deletions may produce no specific phenotype. Consequently, it is conceivable that normal individuals may also carry and propagate sizable deletions in Xq27 → proximal Xq28.

The situation is strikingly different in the gene-rich distal part of Xq28, where only one male deletion appears to cover more than one gene [Kenwrick et al., 1992]. Keeping in mind that females with deletions of Xq28 are fertile [Skibsted et al., 1984; Tharapel et al., 1993], the absence of such deletions in males suggests that they are male-lethal.

The positions and extent of the male deletions reported within Xq27–q28 are presented in Figure 1. Figure 1D depicts possible localization of the loci for syndromic MR whose genes have not yet been cloned. The location of the locus MRX27 [Glass et al., 1991] has been recently adjusted by Gedeon et al. [1996]. Map positions of the locus MRX3 [Gedeon et al., 1991] and the locus postulated by Kondo et al. [1991] could not be altered in this study, as both these conditions manifest as MR only. However, the positions of the genes involved in several MR syndromes can be considerably narrowed, because once a syndrome-specific phenotype is absent in a deleted patient, the respective gene can be excluded from the area of the deletion. Using these criteria, the positions of ANOP1, BD, DKC, IP2, MRSD, OPD1, WSN, BFLS, and ADS can be narrowed down, as depicted on the map (Fig. 1D). The exclusion map presented will facilitate clinical interpretation of contiguous gene syndromes, as well as localization of new loci in the distal Xq.

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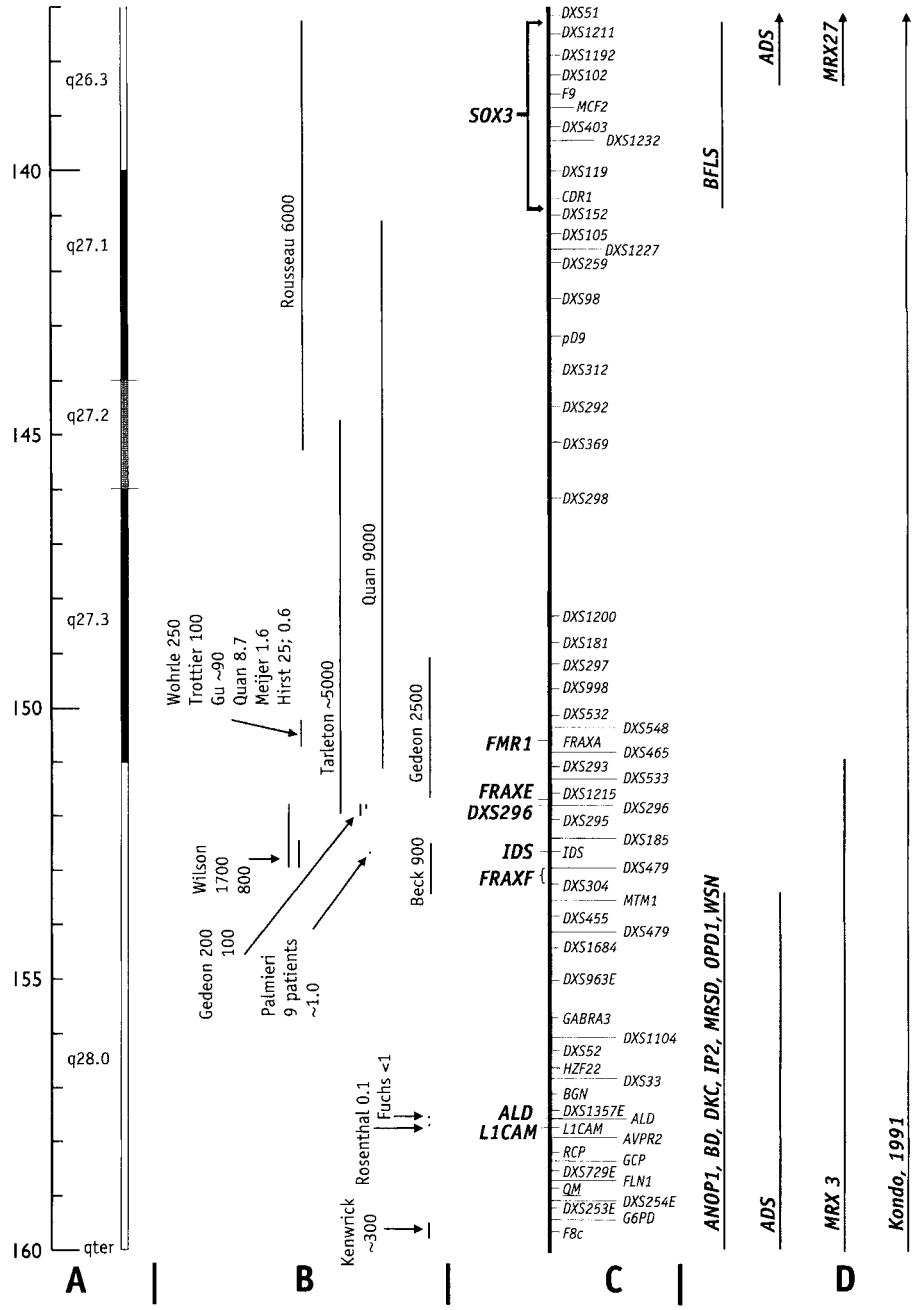

Fig. 1. Male deletions in the distal Xq. **A**: Map of the X chromosome scaled in megabases. **B**: Deletions reported in males are represented by vertical lines, with name of first author and approximate size in kb. **C**: Order of X chromosome markers [Willard et al., 1994.] Bold horizontal symbols indicate position of known genes involved in mental retardation. The position of SOX3 [Stevanovic et al., 1993] has been narrowed (Schmidt, unpublished results) using an X chromosome with a duplication DXS152→Xqter [Schmidt et al., 1991]. **D**: Potential location of loci for the mental retardation syndromes listed below: ANOP1, anophthalmos (Graham syndrome) MIM 301590; ADS, Ataxia-dementia syndrome MIM 301840; BFLS, Börjeson-Forssman-Lehmann syndrome MIM 301900; BD, bullous dystrophy MIM 302000; DKC, dyskeratosis congenita MIM 305000; IP2, incontinentia pigmenti type II MIM 308310; MRSD, mental retardation, skeletal dysplasia (Christian syndrome) MIM 309620; OPD1, otopalatodigital syndrome MIM 311300; WSN, Waisman syndrome (Parkinsonism, Laxova syndrome) MIM 311510. References: Fuchs <1, Sarde et al., 1994; Gedeon 200, 100: Gedeon et al., 1995; Gedeon 2500, Gedeon et al., 1992; MRX3, Gedeon et al., 1991; MRX27, Glass et al., 1991; Gedeon et al., 1996; MTM1, Dahl et al., 1995; SOX3, Stevanovic et al., 1993; Tarleton ~ 5000, Albright et al., 1994; Wilson 1700, 800, Steen-Bondeson et al., 1992; Wohrle 250–Hirst 25; 0.6, Hirst et al., 1995 (deletions reported by de Graaff et al. [1995] are not included in Figure 1, as they result from somatic instability of the expanded FMR1 gene).

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